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ORPHAN DRUGS AND RARE DISEASES: CURRENT LANDSCAPE, CHALLENGES, AND FUTURE PROSPECTS

ARUN KUMAR RAI¹, SHAYAM SINGH MAINA², MONIKA KOURAV², AMRIT LAL PATEL³

¹Assistant Professor, Department of Pharmaceutical Chemistry, Corporate Institute of Pharmacy, Bhopal, Madhya Pradesh, India. (462022)

²Assistant Professor, Surabhi College of Pharmacy, Bhopal Madhya Pradesh, India. (462022)

³Ph. D. Research Scholar, Parul University, Vadodara Gujrat, India

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Abstract

One of the most exciting and revolutionary areas of contemporary pharmaceutical development is orphan pharmaceuticals, therapeutic compounds intended to cure uncommon diseases affecting fewer than 200,000 people in the United States (or comparable populations in other regions). The market for orphan drugs is expected to increase at a compound annual growth rate (CAGR) of 10.94% from its estimated USD 236.27 billion in 2025 to USD 667.48 billion by 2035. This impressive development trajectory is a result of supporting regulatory frameworks, advances in precision medicine and genetic research, and the rising incidence of rare diseases globally. However, the landscape of orphan drugs poses significant obstacles, such as extraordinarily high development and per-patient treatment costs, tiny patient populations that make clinical trial enrollment difficult, and complex regulatory procedures across several jurisdictions. This thorough analysis looks at the state of rare diseases and orphan medications now, summarizes what is known about development obstacles, and considers potential avenues for therapeutic innovation in the future. The study covers market dynamics, legislative implications, technology developments such as gene and cell therapies, regulatory processes and incentives, and clinical trial design concerns. This review offers insights for pharmaceutical researchers, legislators, patient advocacy organizations, and medical professionals involved in managing rare diseases by combining contemporary literature and market statistics.

Keywords: orphan drugs, rare diseases, gene therapy, cell therapy, regulatory frameworks, clinical trials, precision medicine, market dynamics, unmet medical needs.

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*Corresponding Author

Arun Kumar Rai

Assistant Professor, Department of Pharmaceutical Chemistry, Corporate Institute of Pharmacy, Bhopal, Madhya Pradesh, India. (462022)

I. INTRODUCTION

1.1 Definition and Epidemiology

Often referred to as "orphan diseases," rare diseases represent a substantial but often disregarded global public health concern. The Orphan Drug Act (ODA) of 1983 in the United States defines a rare disease as any condition affecting fewer than 200,000 people; in the European Union, rarity is defined as affecting fewer than 5 in 10,000 people; and in Japan, the threshold is roughly 50,000 patients [1]. The National Center for Advancing Translational Sciences estimates that approximately 10,000 rare diseases afflict the US population, with about 25–30 million Americans living with a rare condition [2]. Despite individual rarity, the

collective burden of rare diseases is significant. This means that hundreds of millions of people are impacted worldwide [3].

Rare diseases have a very varied epidemiological distribution. Roughly 75–80% of uncommon diseases are genetically based, and many of them affect children and have a high morbidity and mortality rate [4,5]. Metabolic disorders (e.g., lysosomal storage diseases), genetic blood disorders (e.g., hemophilia, sickle cell disease variants), rare cancers, immunological disorders (e.g., primary immunodeficiencies), and neurological conditions (e.g., spinal muscular atrophy, rare epilepsies) are common categories of rare diseases⁶. Remarkably, rare malignancies account for about 25% of all cancer cases, highlighting the significant overlap between oncology and rare disease treatments [7].

1.2 Historical Context and the Orphan Drug Act

Due to the economic theory that small patient groups could not produce enough income to cover the

significant investments needed for drug research, there was very little pharmaceutical development for uncommon diseases before to 1983. This led to the "therapeutic orphan" problem, where patients with severe illnesses did not have access to appropriate therapies even when scientists were aware of possible remedies [8]. A paradigm change was sparked by the Reagan administration's United States Orphan Drug Act of 1983, which introduced financial and legal incentives to encourage private pharmaceutical investment in treatments for rare diseases [9].

The ODA established multiple incentive mechanisms including:

- Market exclusivity: Seven years of market protection from generic competition following FDA approval
- Tax credits: Up to 25% tax credits on qualified clinical trial expenses
- Fee reductions: Waivers and reductions of regulatory filing fees
- Regulatory flexibility: Enhanced pathways including accelerated approval and breakthrough designation
- Research support: Grants and technical assistance from the FDA's Office of Orphan Products Development

The ODA has had a revolutionary effect. Compared to fewer than 30 in the pre-ODA era, the FDA has authorized nearly 900 orphan medicines since its inception [10]. Orphan drug development has become a global pharmaceutical priority because to similar regulatory frameworks in Japan (Orphan Drug Development Promotion Program, created 1993) and Europe (Advanced Therapy Medicinal Products Regulation, adopted 1999) [11].

1.3 Current Market Overview and Growth Projections

Over the past 20 years, the market for orphan drugs has grown at an exponential rate. According to market estimates, the orphan drug industry is estimated to be worth USD 236.27 billion in 2025 and is expected to grow to USD 667.48 billion by 2035 (CAGR 10.94%) or USD 312.53 billion by 2030 (CAGR 6.24%) [12]. Orphan pharmaceuticals are predicted to account for around one-fifth of global prescription drug sales by 2030; this percentage has increased in the last ten years [13].

Due to advantageous regulations, a strong pharmaceutical infrastructure, and more prevalent awareness, North America presently leads the world market for orphan drugs. However, as healthcare infrastructure advances and diagnostic capacities rise, emerging markets-especially those in Asia-Pacific regions-are seeing faster expansion. Due to the high frequency of rare malignancies (about 25% of all cancer diagnoses), the therapeutic segmentation shows oncology as the leading category, accounting for roughly 38.60% of the market revenue from clinical trials for rare diseases by 2025 [14].

2. CURRENT LANDSCAPE: THERAPEUTIC MODALITIES AND UNMET NEEDS

2.1 Evolution of Therapeutic Modalities

Therapeutic techniques for orphan drugs have changed significantly. In the past, small-molecule medications made up the majority of orphan drugs [15]. But the technology scene has changed significantly, especially in the last ten years Comparative Evaluation of Therapeutic Modalities for Rare Diseases (Table 1).

Table 1: Comparative Evaluation of Therapeutic Modalities for Rare Diseases.

Therapeutic Modality	Mechanism of Action	Examples	Advantages	Limitations/Challenges	Clinical Status / Applications
Gene Therapy	Introduction, replacement, or modification of defective genes using viral/non-viral vectors	Zolgensma (SMA), Luxturna	Potential for one-time curative treatment; targets root cause	High cost, immune response, delivery challenges, long-term safety unknown	Approved for select monogenic disorders; rapidly expanding
Cell Therapy	Use of living cells (e.g., stem cells, CAR-T cells) to restore or modify function	Kymriah, Yescarta	Long-lasting therapeutic effect; personalized treatment	Complex manufacturing, high cost, safety issues (CRS, neurotoxicity)	Approved in oncology; under investigation for rare diseases
Biologics	Target-specific binding to proteins/pathways involved in disease	Eculizumab, Adalimumab	High specificity, well-established platform, faster development	Expensive, requires repeated dosing, immunogenicity	Widely used in rare immune and genetic disorders
Small Molecule Drugs	Modulate specific molecular targets (enzymes, receptors, pathways)	Ivacaftor (CF), Risdiplam (SMA)	Oral availability, lower cost vs biologics, easier manufacturing	Limited to certain targets, off-target effects	Still dominant in many rare diseases

Precision Medicine	Based on genetic/molecular profiling of patients	NTRK inhibitors, EGFR inhibitors	Personalized treatment, improved efficacy	Requires advanced diagnostics, small patient subsets	Growing in rare cancers and genetic diseases
RNA-based Therapies	Modulate gene expression at RNA level	Spinraza (SMA), Patisiran	Highly specific, useful for previously undruggable targets	Stability issues, delivery challenges, repeated dosing	Rapidly emerging field
Enzyme Replacement Therapy	Replaces deficient or absent enzymes	Imiglucerase (Gaucher disease)	Effective for metabolic disorders, improves quality of life	Lifelong therapy, high cost, limited tissue penetration	Standard treatment for lysosomal storage diseases

Gene Therapy Advances: The frontier of treating rare diseases is represented by gene therapy platforms¹⁶. With mechanisms targeting monogenic illnesses such as spinal muscular atrophy (Zolgensma), aromatic L-amino acid decarboxylase (AADC) deficiency (KEBILIDITM), Fabry disease, and different hemophilias, adeno-associated virus (AAV) vector-based gene treatments have gained particular importance⁸. High hopes for breakthrough potential in extremely rare disorders are reflected in the gene therapy segment's 2.1 percentage point contribution to the orphan medication market's compound annual growth rate¹³. Although there are still issues with vector immunogenicity, impact persistence, and manufacturing scalability, FDA approvals for gene treatments increased in 2024–2025 and several innovative drugs entered the clinic [16].

Cell Therapy Innovations: Another fastgrowing approach is cell treatments, such as stem cell-derived medicines and CAR-T cell therapies for hematologic malignancies. These methods have the potential to produce long-lasting therapeutic benefits, but accessibility is severely hampered by manufacturing complexity and cost issues⁶.

Biologics and Monoclonal Antibodies: Recombinant proteins and monoclonal antibodies continue to be the most popular approaches for orphan indications, especially in uncommon inflammatory and immunological disorders. These platforms' maturity allows for comparatively quick development schedules.

Small Molecules and Precision Therapeutics: Small compounds continue to be important despite competition from new techniques, especially when it comes to targeting certain mutations and metabolic diseases. Pharmacogenomic data is rapidly being used by precision medicine methods to create highly focused small medicines for genetically determined disease subsets [6].

2.2 Unmet Medical Needs in Rare Diseases

Despite therapeutic progress, substantial unmet medical needs persist across rare disease domains:

Diagnostic delays: Many uncommon diseases take five to seven years to properly diagnose, during which time

patients develop neurological impairment and organ deterioration [17].

Absence of approved therapies: There are few FDA-approved treatments for thousands of uncommon disorders, and supportive care is the only available choice [16].

Incomplete therapeutic responses: Rather than curing or modifying the condition, many authorized orphan medications only alleviate symptoms⁶.

Pediatric challenges: Pediatric populations are affected by almost 50% of rare diseases, yet treatment development is especially slow for this group [6].

Disease-modifying therapy gaps: Disease-modifying medicines are still elusive for progressing uncommon diseases, especially neurological disorders [6].

Genetic variants and heterogeneity: The development of treatments is complicated by the significant phenotypic and genotypic heterogeneity that many uncommon diseases exhibit [18].

3. Regulatory Framework and Incentive Mechanisms

3.1 FDA Regulatory Pathways

In order to facilitate the development of orphan drugs, the FDA has established a number of regulatory paths that acknowledge the distinctive features of rare disease drug development [19]:

Orphan Drug Designation (ODD): Demonstrates that the medication cures an illness that affects less than 200,000 US patients or affects more than 200,000 patients but the drug maker cannot fairly expect to recover development and marketing expenses [2]. This is the foundational approach. A clinical justification proving scientific plausibility and possible public health benefit is submitted to start the ODD procedure [2]. Notably, ahead planning and regulatory alignment are made possible by the FDA's approval of ODD submission as early as preclinical development¹⁶.

Breakthrough Therapy Designation: This approach, which was created by the FDA Safety and Innovation Act (FDASIA, 2012), is applicable to medications for serious or life-threatening illnesses when initial data indicates a significant improvement over current alternatives. Expedited review, priority review, and extensive interactive communication with

FDA reviewers are examples of breakthrough classifications. This approach has grown in importance for the development of orphan drugs, especially for gene and cell therapies that address unmet needs in extremely rare illnesses [16].

Accelerated Approval: When a disease is severe and there are no suitable alternatives, this pathway allows approval based on surrogate or intermediate clinical outcomes that are fairly likely to anticipate clinical benefit. Post-approval studies are necessary to verify clinical benefit in cases of accelerated approval. Accelerated approval is a crucial route that gives patients access to potential treatments for numerous rare diseases with high unmet medical need and few options.

Priority Review: For medications that target critical illnesses and show benefits above current therapy, this method leads to FDA review completion within 6 months (compared to usual 10-month timescales) [16].

Regenerative Medicine Advanced Therapy (RMAT) Designation: This pathway, which was created by the 21st Century Cures Act, covers regenerative medicines such as cell therapies, tissue engineering products, and combination products that have the potential to treat severe or fatal illnesses. Accelerated development schedules may be supported by RMAT classification, which speeds up contacts with the FDA [17].

3.2 European Medicines Agency (EMA) Framework

The EMA has established a parallel but distinct regulatory framework for orphan medicinal products in the European Union. Important characteristics consist of:

Orphan Designation: Less than 5 out of 10,000 EU citizens are considered orphans, according to EMA. Submission of scientific justification and proof of potential public health benefits is necessary for the designation procedure.

Marketing Authorization via Centralized Procedure: To ensure uniform evaluation throughout EU member states, all orphan-designated drugs must follow the EMA's centralized approach.

Market Exclusivity: Ten years of market exclusivity are granted to approved orphan drugs; if a pediatric investigative plan (PIP) is approved, this period might be extended to twelve years.

Fee Reductions: For orphan products, the EMA offers lower application and post-approval activity fees, just like the FDA.

Key Regulatory Difference: In order to promote regulatory coherence and clarity before official submission, the EMA mandates pre-submission meetings (scientific advice) for applicants seeking orphan classification [21].

3.3 Comparative Analysis: FDA vs. EMA Harmonization

Significant agreement exists between the FDA and EMA on the designation of orphan drugs, according to an analysis of regulatory decisions²². Regulatory

variance was mostly caused by non-submission or withdrawal rather by substantive disagreement among the 33 orphan novel active drugs licensed by the FDA alone [17]. In order to exchange information on orphan designations, market exclusivity, regulatory flexibility, and clinical trial design optimization, the FDA and EMA continue to collaborate through formal clusters [22].

However, subtle differences persist, particularly regarding:

- Endpoint selection for efficacy demonstration
- Acceptable evidence standards (EMA typically requiring higher quality evidence)
- Post-approval requirements and pharmacovigilance expectations
- Pricing and reimbursement considerations

3.4 Financial Incentives and Tax Credits

One of the most important strategies supporting the feasibility of orphan drug research is financial incentives. FDA-granted tax credits can reduce qualifying clinical trial expenditures by up to 25%, which is a significant incentive considering the average costs associated with developing orphan drugs. Waivers of application fees also lessen the administrative burden of regulations. However, detractors contend that these incentives might not be enough to offset the exceptionally high treatment costs per patient that are a feature of many approved orphan medications, especially gene treatments.

4. CHALLENGES IN ORPHAN DRUG DEVELOPMENT AND COMMERCIALIZATION

4.1 Economic Challenges

Development Costs and Per-Patient Pricing:

The development of orphan drugs involves paradoxical economics. Although development expenses must be recovered from small patient groups, they are nonetheless equivalent to those of mainstream pharmaceutical development (estimated USD 2-3 billion per approved medicine including failures) 4. Extremely high per-patient costs are a result of this economic reality. Gene therapy can cost between USD 1.2 and USD 2.0 million per patient, and orphan medicine prices often surpass USD 300,000 per year¹. These costs raise questions about the sustainability of the healthcare system and significantly impede patient access, especially in environments with little resources [13].

Market Size Constraints: Total addressable markets are naturally limited by small patient populations. There are only 21,000 potential patients for a rare condition that affects 50,000 people worldwide, with a 60% diagnostic prevalence and a 70% treatment initiation rate. This is insufficient for typical pharmaceutical ROI models. Due to this economic reality, access discrepancies result from premium pricing and exclusive distribution methods [4].

Insurance and Reimbursement Barriers: The pricing of orphan drugs is being closely examined by payers, who need strong health economic proof of

their worth. Because there are few therapeutic alternatives and small trial populations, orphan medicines frequently lack comparative effectiveness data. Reimbursement talks are made more difficult by this evidence gap, which may delay or limit patient access. Furthermore, payer sustainability issues are raised by budget impact models for costly orphan medicines, which result in stringent utilization control and prior authorization requirements [23].

4.2 Clinical Trial Design Challenges

Patient Recruitment and Retention: Recruitment for clinical trials is complicated by small patient groups. Finding and recruiting enough people is a major challenge for ultra-rare diseases with fewer than 5,000 patients worldwide. Decentralized trial approaches and increased remote monitoring capabilities are required due to the geographic dispersion of patients with uncommon diseases. Long trial lengths, intrusive procedures, and the stress of repeated visits all contribute to patient retention issues. Patient populations with rare diseases frequently exhibit natural history variability and illness heterogeneity, which makes standardizing and interpreting results more difficult [17].

Natural History Variability: The natural histories of many uncommon diseases vary greatly. Patients with progressive illnesses may exhibit varying rates of progression, making it more difficult to understand the results of treatment. Because many uncommon disorders lack established outcome measures, it is necessary to construct disease-specific scales and endpoints, which takes a long time [22].

Regulatory Endpoint Expectations: When supported by disease pathobiology, regulatory bodies are increasingly accepting surrogate endpoints and patient-reported outcomes (PROs) for uncommon medical situations. However, significant natural history studies are usually necessary before treatment trials in order to demonstrate sufficient scientific justification for endpoints. Development timelines are greatly extended by this sequence [22].

Adaptive Trial Designs: Although there are theoretical benefits to using adaptive trial approaches (platform trials, basket trials, n-of-1 designs) for the development of rare diseases, there are still execution issues. Regulatory guidance regarding permissible adaptive elements continues evolving, and statistical approaches for small populations remain technically complex. However, a positive trend for the effectiveness of orphan drug development is shown by the growing acceptance of these approaches [17].

4.3 Regulatory Challenges

Regulatory Complexity Across Jurisdictions: The FDA, EMA, and other national bodies have different regulatory regimes that necessitate redundant filings and possibly contradictory regulations. Despite efforts to harmonize through ICH norms, there are still significant discrepancies. Sponsors of orphan drugs have to deal with these challenges, which adds time and expense. Smaller businesses creating orphan

medications frequently require outside consulting because they lack regulatory experience [24].

Manufacturing and CMC Compliance: Traditional small-molecule pharmaceutical techniques are not familiar with the manufacturing issues associated with modern orphan medications, especially gene and cell therapies. For cell treatments, Chemistry, Manufacturing, and Controls (CMC) compliance calls for specific knowledge and infrastructure. CMC planning is made more difficult by the ongoing evolution of regulatory requirements for the analytical characterisation of complex biologic products [6].

Post-Marketing Requirements: Ongoing research requirements are imposed by accelerated approval procedures, which demand post-approval confirmatory studies. It is still difficult to effectively meet regulatory requirements for pharmacovigilance in small populations while upholding patient confidentiality and privacy protections [24].

4.4 Scientific and Medical Challenges

Disease Heterogeneity and Personalized Medicine: Rare illnesses frequently manifest as genetic and phenotypic diversity. Personalized treatment approaches that target specific mutations or molecular subtypes may further split patient groups, creating incredibly rare disease categories. Although precision medicine is an effective therapeutic approach, it may exacerbate patient stratification and market fragmentation.

Diagnostic Challenges: Many uncommon diseases have diagnostic delays of five to seven years on average, during which time patients suffer permanent organ loss. Improved diagnostic efficiency is promised by advancements in diagnostic techniques, such as increased newborn screening, whole genome sequencing, and biomarker identification. However, adoption in various healthcare systems is still lacking, especially in environments with limited resources.

Limited Natural History Data: Comprehensive natural history studies that describe illness course, prognostic variables, and outcome trajectories are lacking for many rare diseases. Clinical trial design becomes speculative and regulatory endpoint justification becomes difficult in the absence of solid natural history data. The creation of prospective observational cohorts and illness registries is a continuous priority.

5. TECHNOLOGICAL INNOVATIONS AND EMERGING THERAPEUTIC MODALITIES

5.1 Gene Therapy Revolution

The most revolutionary therapeutic development in the last ten years for the treatment of uncommon diseases is gene therapy. The FDA has approved AAV-mediated gene replacement therapy for a number of conditions:

Spinal Muscular Atrophy (Zolgensma): In 2019, the FDA authorized Onasemnogene abeparvovec (Zolgensma), an AAV9 vector containing the survival

motor neuron (SMN1) gene, as the first approved gene therapy for SMA Type I. Zolgensma shows exceptional clinical benefit, turning SMA Type I from a consistently deadly illness into a controllable condition with significant improvement in survival and function. However, Zolgensma set new standards for orphan medication pricing at about USD 2.125 million per patient, which sparked considerable policy attention.

AADC Deficiency (KEBILIDI™): KEBILIDI™ is an AAV5-mediated gene therapy for aromatic L-amino acid decarboxylase deficiency, an extremely rare neurometabolic illness that affects less than 100 people worldwide. It was authorized by the FDA in 2024 under accelerated approval. The approval reflects the wider potential of gene therapy for genetically specified illnesses and shows the FDA's dedication to ultra-rare disease treatments.

Hemophilia: In 2022, the FDA approved eteplirsen (roctocog alfa) for hemophilia B after it demonstrated markedly increased clotting factor levels and fewer bleeding incidents with a single injection. Clinical development has begun for a number of AAV-based gene therapies for hemophilia B. These developments may change the trajectory of the illness rather than only treating its symptoms [6].

Inherited Retinal Diseases

Technical Challenges and Future Directions:

Continued gene therapy development faces several technical challenges:

Vector immunogenicity: Immune-mediated toxicity and reduced transduction effectiveness can result from pre-existing or acquired immunity to AAV vectors.

Durability concerns: For many therapeutic treatments, the endurance of long-term transgenic expression is still not fully understood.

Manufacturing scalability: Large-scale production is hampered by the current AAV manufacturing techniques, which are especially important as signals spread to bigger populations.

Off-target effects: Despite present evidence of positive safety profiles, further research is necessary to address potential genomic integration hazards and off-target mutagenesis.

CNS penetration: Although intrathecal and intracerebroventricular administration methods are improving, obtaining sufficient CNS transduction for neurological illnesses is still difficult.

5.2 Cell Therapy Advances

CAR-T Cell Therapies: For hematologic malignancies, chimeric antigen receptor T-cell (CAR-T) treatments have shown dramatic therapeutic benefit, especially in chronic lymphocytic leukemia and relapsed or refractory B-cell lymphomas. Tisagenlecleucel (Kymriah), axicabtagene ciloleucel (Yescarta), and other FDA-approved CAR-T treatments have been shown to achieve complete remission rates above 50% in treatment-refractory populations. However, widespread use is hampered by manufacturing complexity, the need for cellular customization, and

the dangers of neurotoxicity and cytokine release syndrome.

Stem Cell Therapies: For a number of uncommon diseases, such as hemophilia, degenerative neurological disorders, and graft-versus-host disease (GVHD), mesenchymal stem cells (MSC) and other stem cell-based treatments are beginning clinical research. However, compared to small-molecule or biologic routes, cell therapy regulatory pathways are still less developed, and manufacturing uniformity continues to be a concern [17].

6. CLINICAL TRIAL DESIGN AND METHODOLOGICAL INNOVATIONS

Genomic, proteomic, and metabolomic data are increasingly being used in precision medicine techniques to target certain molecular changes and identify disease subtypes. Rare cancer treatments have benefited greatly from this strategy, as focused medications that target particular mutations (such as EGFR mutations, ALK rearrangements, and NTRK fusions) have improved prognoses in particular patient populations. Precision medicine, however, paradoxically exacerbates development issues by simultaneously fragmenting populations and establishing ultra-rare illness categories with even smaller treatment populations.

6.1 Adaptive Trial Designs

Adaptive trial designs represent methodological advances particularly suited to rare disease development. These methods consist of:

Platform Trials: Compared to sequential individual trials, umbrella platforms allow for the quick evaluation of several therapies or patient subgroups under shared disease frameworks, saving time and resources.

Basket Trials: mechanisms that increase recruitment and statistical power by allowing patients from a variety of uncommon diseases that are connected by common genetic drivers (such as NTRK fusion-positive solid tumors, regardless of initial malignancy).

N-of-1 Trials: Single-subject designs allow for the assessment of therapeutic interventions in individual individuals, which is especially important for extremely rare illnesses that only impact a small number of people worldwide.

Response-Adaptive Randomization: mechanisms that optimize statistical power and ethical resource allocation by allowing real-time adjustment of treatment allocation probability based on new safety and efficacy data.

6.2 Decentralized and Remote Trial Models

COVID-19 accelerated adoption of decentralized trial models incorporating:

- Remote patient monitoring through wearable devices and telehealth platforms
- At-home blood draws and specimen collection
- Expanded informed consent processes through electronic consent platforms
- Virtual study visits reducing patient burden

Patients with rare diseases, who frequently encounter geographical obstacles while trying to reach specialized medical facilities, stand to gain the most from these developments. However, data quality and regulatory compliance issues brought forth by remote monitoring necessitate cautious handling [25].

7. MARKET DYNAMICS AND COMMERCIALIZATION STRATEGIES

In contrast to conventional randomized controlled trials, increasing the use of real-world evidence (RWE) from electronic health records, illness registries, and patient cohorts allows for larger populations and longer follow-up. Registries that record the natural history, prognostic variables, and outcomes of uncommon diseases offer crucial information that supports trial design choices and regulatory goals. An underappreciated but vital infrastructure goal is funding disease-specific registries.

7.1 Market Segmentation and Growth Drivers

Therapeutic Area Growth: Due to the high frequency of rare cancers (25% of all diagnoses) and significant investment in targeted therapeutics, oncology leads rare disease clinical trials and pharmaceutical development, accounting for 38.60% of market revenue. Neurological and immunological disorders continue to be underrepresented in relation to disease burden, whereas metabolic disorders and hematologic conditions constitute secondary growth areas [25].

Geographic Expansion: Because of its strong pharmaceutical infrastructure, advantageous regulations, and increased awareness of diagnostic incidence, North America presently leads the world market for orphan drugs. However, as healthcare systems evolve, regulatory frameworks emerge, and diagnostic capabilities grow, Asia-Pacific regions are seeing faster expansion. Opportunities abound in emerging nations, but there are drawbacks as well, such as unequal drug availability and price pressure [13].

Technological Drivers: High expectations for treatments for ultra-rare diseases are reflected in the orphan drug market's CAGR, which is increasing by about 2.1 percentage points thanks to innovative gene and cell therapy platforms. These innovative modalities demand higher prices, but they also raise concerns about cost-effectiveness.

7.2 Competitive Dynamics and "Evergreening" Concerns

As orphan drug pipelines develop, more and more rival medications are aimed at the same indications. The FDA authorized 20–25 new orphan medications every year between 2020 and 2024; by 2030, 160–200 more approvals are anticipated. Several dynamics are produced by this escalation of competition:

Evergreening and Exclusivity Gaming: Potential "ever greening" tactics, in which sponsors create several orphan indications for mass-market medications to prolong exclusivity periods after initial

approvals, have been uncovered by regulatory investigations. Investigations by the Government Accountability Office and congressional scrutiny point to the necessity of improved oversight procedures.

Competition Within Indications: Multiple gene therapies that target the same illnesses (e.g., several hemophilia B therapies under development) increase market competition while dividing patient groups that are already small, thereby jeopardizing the profitability of all competitors.

Pricing Pressures: The price of orphan drugs is under growing pressure from competition. Negotiation positions are strengthened by payer demands for comparative effectiveness evidence and health economic data. In contrast to past trends, early evidence indicate that orphan medicine pricing growth may be moderate [26].

7.3 Patient Access Programs and Innovative Contracting

In order to handle payer concerns and promote access, pharmaceutical firms are increasingly implementing outcomes-based contracting, managed access agreements, and patient support programs. Among these innovations are:

- Risk-sharing agreements linking payment to clinical outcomes
- Installment payment plans reducing upfront costs
- Patient assistance programs providing drugs at reduced cost to financially vulnerable patients
- Compassionate use and expanded access programs enabling pre-approval access
- Direct-to-consumer partnerships bypassing traditional payers

These initiatives improve patient access, but they also add complexity and administrative strain to healthcare systems.

8. POLICY IMPLICATIONS AND FUTURE PROSPECTS

8.1 Orphan Drug Policy Reforms

Tensions between ensuring fair patient access (addressing affordability and sustainability) and rewarding innovation (supporting medication research through exclusivity and price freedom) are reflected in current policy discussions. Among the suggested changes are:

Exclusivity Limitations: Potential legislative changes include proposals to restrict the duration of exclusivity for orphan drugs or to stop "evergreening" by extending exclusivity for broadened indications. However, these changes run the danger of decreasing incentives for the development of orphan drugs, necessitating careful consideration.

Price Negotiation Mechanisms: The Inflation Reduction Act's enhanced payer authority for price negotiation for Medicare beneficiaries may put orphan medications under mild pricing pressure, which could have an impact on producer incentives.

Tax Credit Enhancement: On the other hand, higher orphan drug tax credits might counteract the

effects of pricing pressure on manufacturing incentives, promoting further acceleration of research.

International Harmonization: Streamlined development and decreased redundancy are promised by improved regulatory harmonization through ICH and FDA-EMA cooperation. Positive trends are represented by ongoing initiatives that promote parallel evaluation and mutual appreciation [29].

8.2 Addressing Rare Disease Health Disparities

Patients with rare diseases experience significant access inequities, especially in settings with low resources. Priorities for policy should include:

Diagnostic Infrastructure: Increased access to genetic sequencing, telemedicine diagnostic support, and increased newborn screening are examples of investments in diagnostic capacity that could shorten diagnostic delays and allow for earlier treatment action.

Equitable Pricing Models: While preserving manufacturer incentives in higher-income areas, international reference pricing and tiered pricing systems could provide access for patients in lower-income nations.

Patient Advocacy and Disease Awareness: Through registries and observational cohorts, strengthened patient advocacy organizations play vital roles in disease awareness, patient support, and evidence generation [18].

8.3 Future Therapeutic Prospects and Unmet Needs

Future orphan drug development promises remain substantial:

Ultra-Rare Disease Expansion: As genetic information and customized medical techniques advance, more precise disease subtypes will be found, increasing the number of populations that can be treated with precision therapies. Clinical advancements in extremely rare disorders will be fueled by gene therapy, cell therapy, and RNA therapies.

Neurodegenerative Disease Frontiers: There are significant unmet needs in neurological illnesses, especially progressive neurodegenerative diseases. Therapeutic advancements are anticipated as long as blood-brain barrier penetration technologies, intrathecal administration methods, and neuroprotective mechanisms continue to evolve. Significant therapy prospects exist for rare neurodegenerative disorders such as rare epilepsies, hereditary spastic paraplegias, and spinocerebellar ataxias.

Genetic Medicine Expansion: Exon-skipping techniques for diseases like Duchenne muscular dystrophy, in-vivo gene correction methods, and CRISPR-based gene editing technologies are cutting-edge strategies with significant therapeutic potential. These technologies provide the possibility of curing disorders that were previously deadly or extremely incapacitating, as well as disease modification.

Combination Approaches: Gene therapy may be more effective if it is combined with other modalities (e.g., sequenced immune system modification before

cell therapy, or simultaneous gene replacement with cellular differentiation factors).

Extended Access and Real-World Monitoring: More precise evaluation of therapy response and disease progression will be possible with ongoing advancements in wearable biosensors, digital health platforms, and remote monitoring technologies. This will facilitate adaptive treatment plans and outcome optimization.

9. CASE STUDIES: EXEMPLAR ORPHAN DRUG SUCCESS STORIES AND EMERGING CHALLENGES

9.1 Spinal Muscular Atrophy (SMA)

Spinal muscular atrophy serves as an example of both current issues and the success of orphan drugs. In the past, SMA Type 1 was a consistently fatal illness that caused severe muscle weakness and respiratory failure in newborns by the time they were 6 to 12 months old. Nusinersen (Spinraza, antisense oligonucleotide approved 2016), onasemnogene abeparvovec (Zolgensma, AAV gene therapy approved 2019), and risdiplam (Evrysdi, small molecule approved 2020) are three separate therapeutic approaches that have emerged within the last five years, turning SMA from a fatal condition into a treatable illness [3]. However, competitive dynamics and pricing scrutiny are created by the existence of numerous competing medicines for a small patient pool (~400–500 US SMA Type 1 births annually). Despite having different cost structures and efficacy characteristics, all three treatments show therapeutic benefit. This instance illustrates the paradoxes caused by numerous competing treatments for extremely rare disorders as well as the extraordinary success of orphan drug incentive mechanisms.

9.2 Hemophilia B Gene Therapy

Hemophilia B (factor IX deficiency) gene treatments are cutting-edge strategies with the potential to change the course of the disease. When compared to factor replacement therapy, eteplirsen and other hemophilia B gene therapies significantly normalize factor IX levels with a single infusion, lowering the need for preventive infusions and enhancing quality of life [1]. Nevertheless, there are still issues with manufacturing scalability, unknown long-term durability, and inconsistent clinical results. These treatments demonstrate the potential of gene therapy techniques as well as their ongoing difficulties.

10. CONCLUSION AND DISCUSSION

One of the most active areas of modern pharmaceutical development is the orphan drug landscape, which is marked by quick innovation, changing legal requirements, and ongoing difficulties with fair patient access. The market for orphan drugs is expected to increase to USD 667.48 billion by 2035 due to significant investments in treatments for uncommon diseases, which are fueled by disruptive technologies including gene and cell therapies,

precision medicine techniques, and growing genetic knowledge.

Despite remarkable achievements, substantial challenges persist:

Economic Paradoxes: Development costs are still similar to those of mainstream drugs, but they must be recovered from small patient groups, which results in incredibly high per-patient prices that impede access and raise questions about the sustainability of the healthcare system.

Clinical Trial Complexity: Clinical trial design and regulatory endpoint formulation are complicated by small patient populations, disease heterogeneity, and diagnostic difficulties. Essential priorities include ongoing methodological innovation through decentralized models, adaptable designs, and integration of real-world evidence.

Regulatory Harmonization: Despite improvements in FDA-EMA cooperation, significant jurisdictional disparities still exist. Improved methods for mutual recognition and harmonization could simplify development and cut down on duplication.

Equity and Access: Patients with rare diseases experience significant access inequities, especially in settings with low resources. Important priorities include patient advocacy, fair pricing practices, and policy initiatives that support diagnostic infrastructure.

Future Innovation: Significant therapeutic success is anticipated if gene therapy, cell treatment, RNA therapies, and precision medicine techniques continue to advance. However, persistent investment in disease registries, research infrastructure, and the development of regulatory guidelines is necessary to realize this promise.

The field of orphan drugs is at a turning moment. Advances in genetics, cell biology, and bioinformatics have made it possible to design disease-modifying treatments for disorders that were previously incurable. Concerns about access fairness and growing prices necessitate legislative changes that strike a balance between patient access and innovation incentives. Whether the orphan drug revolution delivers its promise of revolutionizing patient treatment for rare diseases worldwide will depend on how these conflicts are resolved through careful regulatory frameworks, ongoing technical innovation, and stakeholder collaboration.

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CONFLICT OF INTEREST

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ETHICAL APPROVAL

This study does not involve human participants or animals; therefore, Ethical approval was not required.

AUTHORS CONTRIBUTION

The review research was conceived and constructed by Arun Kumar Rai, who drafted the general framework and the initial paper draft. Monika Kourav and Shyam Singh Maina carried out a thorough search of the literature, gathered and arranged pertinent information, and helped write and organise the review many sections. Amrit Lal Patel helped with data analysis, literature review, and paper rewriting for clarity and scientific accuracy. The final text was reviewed, edited, and approved by all authors.

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